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(71) 出願人 (米国を除く全ての指定国について): 第一製薬株式会社 (DAIICHI PHARMACEUTICAL CO., LTD.) [JP/JP]; 〒103-8234 東京都中央区日本橋3丁目14番10号 Tokyo (JP).

(72) 発明者; および

(75) 発明者/出願人 (米国についてのみ): 吉野利治 (YOSHINO, Toshiharu) [JP/JP]. 永田 勉 (NAGATA, Tsutomu) [JP/JP]. 萩野谷憲康 (HAGINOYA, Noriyasu) [JP/JP]. 吉川謙次 (YOSHIKAWA, Kenji) [JP/JP]. 菅野英幸 (KANNO, Hideyuki) [JP/JP]. 永持雅敏 (NAGAMOCHI, Masatoshi) [JP/JP]; 〒134-8630 東京都江戸川区北葛西1丁目16-13 第一製薬株式会社 東京研究開発センター内 Tokyo (JP).

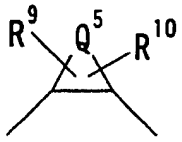
(74) 代理人: 有賀三幸, 外(ARUGA, Mitsuyuki et al.); 〒103-0013 東京都中央区日本橋人形町1丁目3番6号 共同ビル Tokyo (JP).

(81) 指定国 (国内): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK,

[続葉有]

(54) Title: ETHYLENEDIAMINE DERIVATIVES

(54) 発明の名称: エチレンジアミン誘導体



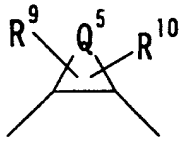
(2)

(57) Abstract: Compounds of the general formula (1): Q^1-Q^2-C(=O)-N(R^1)-Q^3-N(R^2)-T^1-Q^4; and drugs which contain the compounds and are efficacious for thrombosis and embolism. In said formula, wherein R^1 and R^2 are each H or the like; Q^1 is an aromatic ring, a heterocycle, or the like; Q^2 is a single bond, an aromatic ring, a heterocycle, or the like; Q^3 is a group of the general formula (2), or the like; Q^4 is an aromatic ring, a heterocycle, or the like; and T^1 is -CO- or -SO_2-.

(57) 要約:

本発明は式（１）

$Q^1-Q^2-C(=O)-N(R^1)-Q^3-N(R^2)-T^1-Q^4$ （１）

（式中、R^1およびR^2はHなど；Q^1は芳香環、複素環など；Q^2は単結合、芳香環、複素環など；Q^3は  など；Q^4は芳香環、複素環など；T^1は－ＣＯ－または－ＳＯ$_2$を示す）

で表される化合物およびこれを含有する血栓症、塞栓症に有効な医薬に関する。

WO 01/74774 A1

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CR   2003-247888 [24]; 2003-312743 [30]
TI   New diamine compounds are activated blood factor X inhibitors used for
     treating e.g. cerebral or myocardial infarction and angina.
PA   (DAUC) DAIICHI PHARM CO LTD
PI   WO 2003000657   A1 20030103 (200325)* JA  788    C07D209-42     <--
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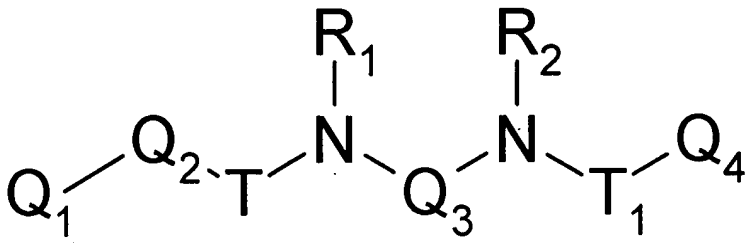
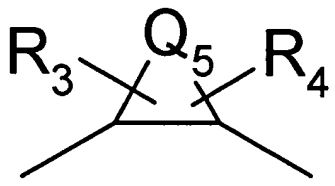


(I)



(i)

TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preparation: (I) Are prepared e.g. by reacting an amine of formula (IV) with an acid of formula (V).

AB WO2003000657 A UPAB: 20030513

NOVELTY - Diamine compounds (I) are new.

DETAILED DESCRIPTION - Diamine compounds of formula (I) and their salts, solvates and N-oxides are new. R1, R2 = H, OH, alkyl or O-alkyl; Q1 = 5-6C carbocyclyl, 5-7 membered heterocyclyl or bi- or tri-cyclic carbocyclyl or heterocyclyl (all optionally unsaturated and optionally substituted);

Q2 = a bond, or divalent 5-6C carbocyclyl, 5-7 membered heterocyclyl or bi- or tricyclic carbocyclyl or heterocyclyl (all optionally unsaturated and optionally substituted); Q3 = a group of formula (i);

Q5 = 1-8C alkylene, 2-8C alkenylene or (CH2)mCH2ACH2(CH2)n; m, n = 0-3;

A = O, N, S, SO, SO2, NH, ONH, NHNH, SNH, SONH or SO2NH; R3, R4 = H, OH, alkyl (optionally substituted by CN, NH2, NHA, NAA, acyl, acylamino, O-alkyl, OH, COOH, COO-alkyl, NHCOOA, N-alkenylcarbamoyl, N-alkenyl-N-alkyl-carbamoyl, CONHO-alkyl, CON(A)OA, SO2A, CONH2, OCONH2, OCONHA, OCONAA, OCOHet, COHet, Arl, NHSO2alkyl, NHSO2Ar, CONHSO2alkyl, CONHSO2Ar or optionally

substituted CONHA or CONAA), alkenyl, alkynyl, halo, acyl, optionally substituted acylamino, O-alkyl, COOH, COO-alkyl, NHACOOA, NHACOOH, CONH2, CONHA, CONAA, N-alkenylcarbamoyl, N-alkenyl-N-alkyl-carbamoyl, CONHO-alkyl, CON(A)OA, CON(A)3, SO2A, COHet, Ar1, NHSO2alkyl, NHSO2Ar, CONHSO2alkyl, CONHSO2Ar, oxo, OCONH2, aralkoxy, O-alkyl-COOH, acyloxy, SO2Ar, SO2-alkyl-COO-alkyl, SO2-alkyl-COOH, acyl (substituted by COO-alkyl, OH, O-alkyl, halo, COOH, NH2, acyloxy, NH-alkyl, N(alkyl)2, SO2alkyl or optionally substituted CON(alkyl)2, COO-alkyl-O-alkyl or acyloxyalkylsulfonyl, SO2-alkyl-OH, SO2O-alkyl, SO2Het or optionally substituted SO2CON(alkyl)2, or R3 + R4 = 1-5C alkylene, 2-5C alkenylene, 1-5C alkylenoxy or carbonyldioxy;
Het = optionally substituted 3-6C heterocyclyl; Ar1 = aryl or heteroaryl;
Ar = aryl;
Q4 = Ar1, arylalkenyl, arylalkynyl, heteroarylalkenyl or optionally unsaturated bi- or tricyclic carbocyclyl or heterocyclyl (all optionally substituted);
T = CO or CS;
T1 = CO, SO2, COCONR11, CSCONR11, COCSNR11, CSCSNR11, COA1NR12, CONH, CSNH, CONHNH, COA2CO, COA3CONH, COC(=NORa)NRb, CS(=NORa)NRbCON=N, CSN=N or CS;
R11, R12, Rb = H, OH, alkyl or O-alkyl; A1 = optionally substituted 1-5C alkylene; A2 = bond or A1, and
Ra = H, alkyl or alkanoyl.
ACTIVITY - Cerebroprotective; Cardiant; Antianginal; Respiratory; Anticoagulant; Thrombolytic; Vasotropic; Antiinflammatory.
MECHANISM OF ACTION - Factor X Inhibitor. In tests on rats, administration of N1-(4-chlorophenyl)-N2- ((1S,2R,4S)-4-((dimethylamino)carbonyl)-2-(((5-methyl-4,5,6,7-tetrahydrothiazolo(5,4-c)pyridin-2-yl)carbonyl)amino)cyclohexyl)ethanediam ide (Ia) (10 mg/kg orally) reduced blood FXa levels over 4 hours by 62-96%.
USE - As activated blood factor X inhibitors for treating and preventing e.g. cerebral infarction, cerebral embolism, myocardial infarction, angina, pulmonary, embolism, Buerger's disease, deep vein thrombosis, disseminated intravascular coagulation, thrombosis following artificial flap/hip replacement or during external circulation, reocclusion, systemic inflammatory reaction syndrome, multiple organ failure or blood coagulation during blood collection. Dwg.0/0

ABEX

UPTX: 20030410
ADMINISTRATION - Administration of (I) is 0.1-200 (preferably 0.5-100) mg/kg/day orally or by injection.
EXAMPLE - 1-Hydroxybenzotriazole monohydrate (71 mg) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloric acid (100 mg) were added to N-((1Rasterisk,2Sasterisk)-2-aminocyclopropyl))-5- chloroindole-2-carboxamide (108 mg) and lithium 5-methyl-4,5,6,7- tetrahydrothiazolo(5,4-c)pyridine-2-carboxylate (124 mg) in dimethylformamide (3 ml) and the mixture was stirred at room temperature for 8 hours. Work-up including silica gel chromatography (methylene chloride:methanol 10:1) gave 72 mg of N-(1Rasterisk,2Sasterisk)-2-(((5- chloroindol-2-yl)carbonyl)amino)cyclopropyl)-5-methyl-4,5,6,7- tetrahydrothiazolo(5,4-c)pyridine-2-carboxamide hydrochloride.